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Frequency of metastasis to the gastrointestinal tract determined by endoscopy in a community-based gastroenterology practice

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ABSTRACT

Metastasis to the gastrointestinal tract is rare. We performed a retrospective analysis to identify patients with metastatic disease to the gastrointestinal tract using two databases containing pathology results from all endoscopic procedures conducted by nearly 200 gastroenterologists in a community setting over a 14-year period. Forty-nine patients were diagnosed with metastasis to the gastrointestinal tract by endoscopy during the study period. Most were women (71%). The most common metastases to the gastrointestinal tract identified by endoscopy were breast cancers (n = 18), followed by melanomas (n = 12), ovarian cancers (n = 7), kidney cancers (n = 5), prostate cancers (n = 2), lung cancer (n = 1), and pancreatic cancer (n = 1). Three patients had unknown primary sites. Among women, the three leading known primary tumor sites were breast, ovary, and melanoma. Among men, the three leading primary tumor sites were melanoma, kidney, and prostate. The stomach was the most common portion of the gastrointestinal tract involved by metastases. Most affected women and were most frequently encountered in the stomach.

KEYWORDS Breast cancer; endoscopy; melanoma

Cancers most commonly metastasize to lymph nodes, liver, and lungs.[1] Brain and bone are also common metastatic sites. Metastases to the gastrointestinal (GI) tract are rare. Most of these GI metastases are asymptomatic and are detected incidentally by imaging or on autopsy. The most common extra-abdominal tumors that have been reported to metastasize to the GI tract are melanomas, breast cancers, and lung cancers.[2] Though any portion of the GI tract can be the site of a metastasis, the small intestine and stomach are the more commonly reported sites.[3,4] Gilg et al[5] recently reported a retrospective database analysis of 217 patients with so-called secondary tumors of the GI tract seen over 30 years at a large academic medical center in Graz, Austria. Melanoma and breast cancer were the most common primary sites for these 95 metastases to the GI tract via lymphovascular spread. Our retrospective study aimed to elucidate the gender-related incidence of metastatic disease to the GI tract in a community gastroenterology practice and hospital in Texas, consisting of nearly 200 gastroenterologists.

METHODS

We performed a retrospective analysis to identify patients with metastatic disease to the GI tract using two distinct databases containing pathology results from all endoscopic procedures performed by gastroenterologists from Texas Digestive Disease Consultants, a community gastroenterology practice with 160 physicians licensed in Texas and Louisiana, as well as from Texas Health Presbyterian Hospital Dallas, a community hospital in Dallas, Texas, with 19 gastroenterologists on staff during the study period. Data were collected from all consecutive patients diagnosed with GI metastases over a 14-year period (2005 to 2018). Demographic data and patient histories were accessed through electronic health records. The study was approved

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by the institutional review board of Texas Health Resources (1229755-1).

The primary inclusion criterion was the pathologic diagnosis of a non-GI malignancy within the GI tract. Patients were included only if the biopsy had been obtained via an endoscopic procedure. Specimens obtained at surgery were excluded, as were patients with lymphoma and extramedullary leukemia involving the GI tract. The clinical data for each patient were reviewed to confirm that each case was a metastasis. Cases involving direct invasion of a GI organ from an adjacent primary tumor were excluded. The indications for the endoscopic procedure and the presence of known cancers or cancers with already known metastatic disease were obtained from the electronic health records. Endoscopy reports were used to identify the anatomic location of the lesions and to obtain gross descriptions of the lesions, which were then classified as ulcerated, malignant appearing, nodular, polyploid, erythematous, or pigmented.

The biopsies obtained at the time of endoscopy were fixed in formalin and processed routinely; hematoxylin/eosin–stained tissue sections were prepared. Slides were then examined and diagnoses rendered by board-certified pathologists from ProPath, who were located at Texas Digestive Disease Consultants, or by pathologists in the Department of Pathology at Texas Health Presbyterian Hospital Dallas. Additional immunohistochemical stains were used to help establish the origin of the metastatic tumors. CDX2 is a highly sensitive and specific marker for adenocarcinomas of intestinal origin.[6] Thyroid transcription factor-1, expressed in the epithelial cells of the thyroid gland and lung, was used to identify lung adenocarcinomas.[7] Though both lung and breast adenocarcinomas can express estrogen receptor and HER2, other markers such as GATA3 were utilized to distinguish breast adenocarcinomas from other malignancies.[8] A immunohistochemical profile that was positive for CK7 and negative for CK20 and CDX2 supported an ovarian origin of the metastasis.[9] Prostate-specific antigen stains were used to classify prostate adenocarcinomas.[10] PAX8 is frequently positive with metastatic tumors of renal origin.[11] SOX10 and Mart 1 immunohistochemistry stains are helpful to confirm the diagnosis of melanoma.[12]

RESULTS

Forty-nine patients were diagnosed with metastasis to the GI tract from non-GI malignancies during the 14-year study period (3.5 cases/year). Five of these 49 patients had metastases to more than one GI site (range, 2 to 3). Their age at the time of diagnosis of GI metastases averaged 63 years (range, 41–88 years). Most patients were women (n = 35, 71%; $P = 0.0027$, women vs men by chi-square). Of the 49 patients with GI metastasis, 35 (71%) had a history of a cancer (other than a nonmelanoma skin cancer) prior to their endoscopy, and most of these (n = 34, 69%) had known metastatic disease prior to their endoscopy. In the 35 patients, an average of 5.9 years had elapsed between the previous diagnosis of cancer and the endoscopy with the identification of a metastasis (range, 0–24 years; interquartile range, 1.5–7 years). In the other 14 patients, the GI metastases were the first manifestation that the patient had cancer, most often breast cancer *(Table 1)*.

Table 1. Primary cancer sites, if known, in patients with no known malignancy prior to the endoscopy showing gastrointestinal metastases

Primary cancer site	*N*
Breast	6
Ovary	2
Melanoma	1
Kidney	1
Pancreas	1
Unknown	3
Total	14

Indications for endoscopy were driven by the patient's signs and symptoms or by abnormal imaging procedures and are listed in *Supplemental Table 1*. In three cases, metastases to the colon or rectum were detected at the time of colorectal cancer screening by colonoscopy.

In just over one-third of the patients (n = 17, 34.7%), ulcerated lesions were seen by the endoscopist (*Supplemental Table 2*). The lesion was described as malignant appearing or infiltrative in 13 other patients (26.5%), and in 7 cases the lesion appeared polypoid. Several examples of metastasis to the GI tract are shown in *Figures 1 and 2*, categorized by endoscopic appearance.

As shown in *Figure 3*, the most common site for the 49 metastases to the GI tract were breast cancers (n = 18, 37%), followed by melanomas (n = 12, 25%). Metastasis from ovarian cancers (n = 7, 14%), kidney cancers (n = 5, 10%), unknown primary site (n = 3, 6%), prostate cancers (n = 2, 4%), lung cancer (n = 1, 2%), and pancreatic cancer (n = 1, 2%) accounted for the other cases. The primary site differed considerably in women and men *(Figure 3b)*. In women, the three leading primary tumor sites were breast, ovary, and melanoma. In men, the three leading primary tumor sites were melanoma, kidney, and prostate.

As shown in *Table 2*, the stomach was the most involved portion of the GI tract, followed closely by the colon. Seven cases involved the duodenum or more distal small bowel, in all cases the jejunum. Results for women and men are shown separately in *Supplemental Tables 3 and 4*.

DISCUSSION

This retrospective series is, to our knowledge, the first to describe metastasis to the GI tract in a community-based gastroenterology practice. Metastasis was most commonly

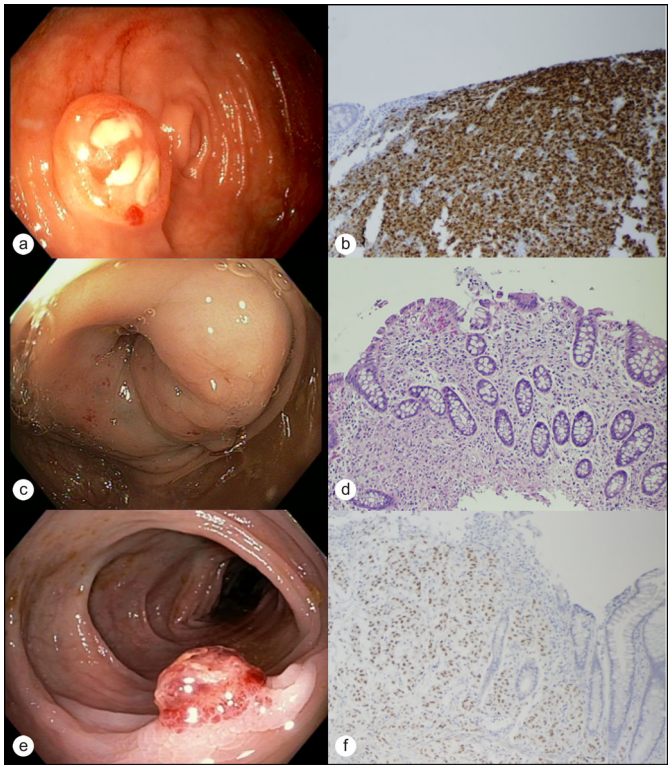

Figure 1. Examples of metastatic tumors to the gastrointestinal tract, categorized by endoscopic appearance. **(a)** Melanoma metastatic to the colon. Raised nonpigmented mass with umbilical ulceration in the cecum. **(b)** Histopathology showing ulcerated colonic mucosa with underlying sheets of highly atypical malignant cells with prominent nucleoli and immunoreactivity for SOX10 (original magnification ×100). **(c)** Breast cancer metastatic to the colon. Infiltrative and circumferential mass with overlying normal mucosa in sigmoid colon. **(d)** Histopathology showing invasive adenocarcinoma (hematoxylin and eosin, original magnification ×100) that had a positive immunostain for the estrogen receptor. **(e)** Renal cancer metastatic to the colon. Erythematous polypoid mass in the transverse colon. **(f)** Histopathology showing neoplastic cells invading colonic mucosa with immunoreactivity for PAX8 (original magnification ×100).

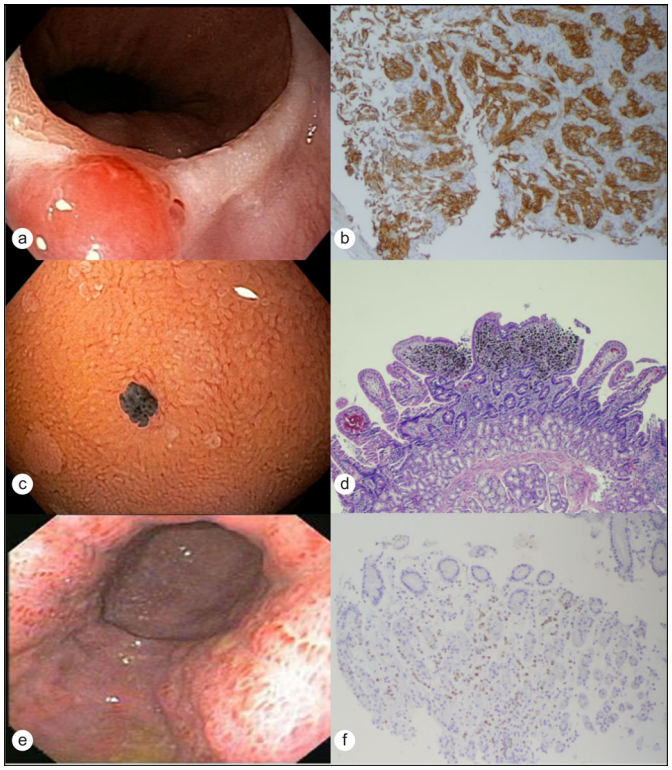

Figure 2. Additional examples of metastatic tumors to the gastrointestinal tract, categorized by endoscopic appearance. **(a)** Renal cancer metastatic to the esophagus. Erythematous nodule in distal esophagus. **(b)** Histopathology showing malignant cells with immunoreactivity for PAX8 (original magnification ×100). **(c)** Melanoma metastatic to the duodenum. A pigmented nonbleeding lesion in the duodenal bulb. **(d)** Histopathology showing neoplastic cells in a sheet-like pattern within duodenal mucosa and immunoreactivity for SOX10 (hematoxylin and eosin, original magnification ×100). **(e)** Breast cancer metastatic to the stomach. Diffuse erythema in a mosaic pattern in the fundus and body of stomach. **(f)** Histopathology showing fragments of stomach demonstrating a neoplastic infiltrate in the lamina propria and immunoreactivity for estrogen receptor (original magnification ×100).

detected in the stomach and colon, probably because these organs were examined most frequently via endoscopy. In contrast, radiologic and autopsy studies have found that the small bowel is the most involved GI site of metastasis.[13,14] Only 26.5% of GI metastases had a malignant or infiltrative endoscopic appearance, stressing the importance of biopsy of visible lesions during endoscopy.

The average interval between the initial diagnosis of cancer and diagnosis of a GI metastasis was just under 6 years for those 35 patients who had a known cancer prior to endoscopy. In contrast, the mean interval recorded by Gilg et al was just over 2.5 years, but this shorter interval included tumors that had spread to the GI tract from adjacent cancers by direct extension.[5] In our study, the longest interval occurred in a patient who was diagnosed with a melanoma 24 years prior to finding a melanoma metastasis to the colon. Late detection of metastatic melanoma is not uncommon.[15,16]

Although metachronous or synchronous GI metastases from GI primary sites (e.g., colon metastasis from gastric adenocarcinoma or gastric metastasis from colorectal adenocarcinoma) are rare, they are likely underdiagnosed because they may be thought to be primary GI cancers.[17–19] Metastases from colorectal cancer most commonly involve the small bowel, but there are reports of metastases to the stomach and ileum.[20] GI metastases from GI primary sites were not included in our study.

Though malignant melanoma can target any portion of the GI tract, radiologic and autopsy studies indicate that the small intestine is the most frequent GI organ involved, possibly due to its greater mass and blood supply.[14,15] Presentations vary depending on tumor size and locations, ranging from vague nonspecific GI symptoms to hollow viscous perforation.[21,22] In our study, only 4 of 14 of patients (28%) with metastatic melanoma to the GI tract had pigmented lesions described during endoscopy *(Figure 2c, 2d)*.

Though metastatic breast cancer to the GI tract is rare, it accounted for the majority of the GI metastases in our study and contributed to the female preponderance we observed.[23] The interval between the initial diagnosis of breast malignancy and subsequent metastasis to the GI tract averaged 9.0 years (range, 1–22 years). The longest previously reported interval was 19 years.[24] Two patients in the current study were diagnosed with breast cancer 21 and 22 years prior to endoscopy showing metastasis. Thus, our study includes the longest reported time interval between primary breast cancer and GI metastatic disease. Such patients are typically treated with chemotherapy, because they usually have widespread disease at the time of diagnosis of the GI metastasis.[25] Because all three patients with unknown primary cancer sites in our study were women with CDX2-negative adenocarcinomas, it is possible that some or all of these patients had metastatic breast (or ovary) adenocarcinoma.

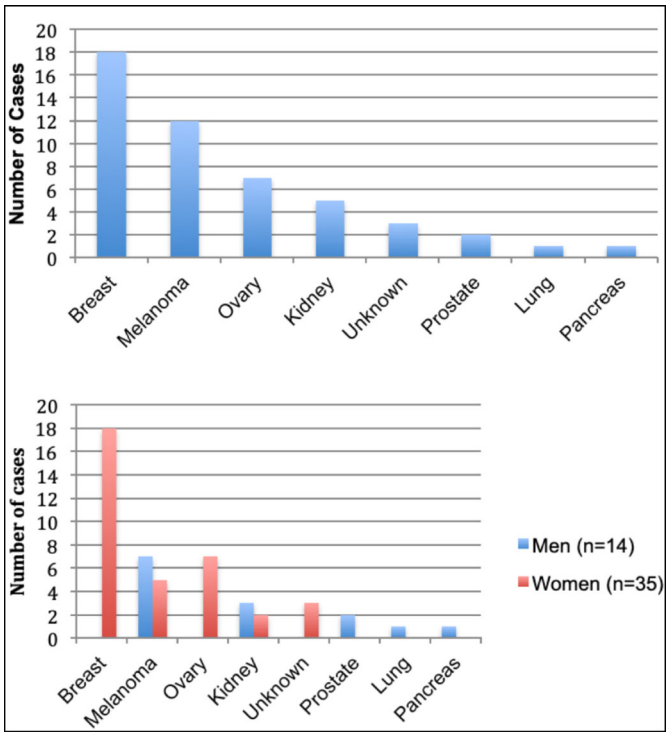

Figure 3. Metastases to the gastrointestinal tract **(a)** identified by primary cancer and **(b)** categorized by gender.

Previous reports suggest that lung cancer is one of the most frequent metastatic malignancies to the GI tract, but the majority of these reports were based on autopsies.[1,26] In our study, only one patient (2%) was diagnosed with a lung cancer metastasis (to the small bowel). Gilg et al observed a 5% prevalence of lung cancer in their secondary GI tumor series.[5] The relatively low incidence of metastasis from lung cancer is likely due to the poor prognosis and short survival associated with metastatic lung cancer. When GI metastases from lung cancer occur, they are most commonly found in the small intestine. It has been postulated that lung cancer can also metastasize to the stomach by swallowing sputum containing malignant cells.[27]

Figure 4 plots the relative incidences of selected cancers in the US (2012–2016)[28] compared to the relative incidences of GI metastases we observed (2005–2018), by primary site in men and women. Compared to the overall incidences of these various cancers, melanoma, kidney cancer, and perhaps pancreas cancer were overrepresented in the men with GI metastases. Breast cancer, ovary cancer, melanoma, and perhaps kidney cancer were overrepresented in the women with GI metastases. Approximately half were from breast cancer.

Our study represents the first series of metastasis to the GI tract in a large community practice. Previous studies and reports were autopsy studies or clinical studies predominantly including patient populations from academic medical centers.[5,29] Furthermore, our study included only patients with metastasis to the GI tract by lymphovascular spread, whereas Gilg et al included many patients who had tumor spread by direct invasion.[5] Gilg et al also included metastasis from

Table 2. Site of metastasis to the gastrointestinal tract, by primary cancer (n = 49)[a]

Malignancy	Esophagus	Stomach	Duodenum	Small bowel	Colon	Rectum	Total
Breast	0	10	0	1	8	1	20
Melanoma	0	7	1	2	4	0	14
Ovary	0	3	0	0	4	0	7
Kidney	2	2	0	0	1	0	5
Prostate	1	0	0	0	1	0	2
Lung	0	0	0	1	0	0	1
Pancreas	0	0	0	0	1	0	1
Unknown	0	1	2	0	1	0	4
Total	3	23	3	4	20	1	54

[a]Five patients had metastasis to more than one gastrointestinal site.

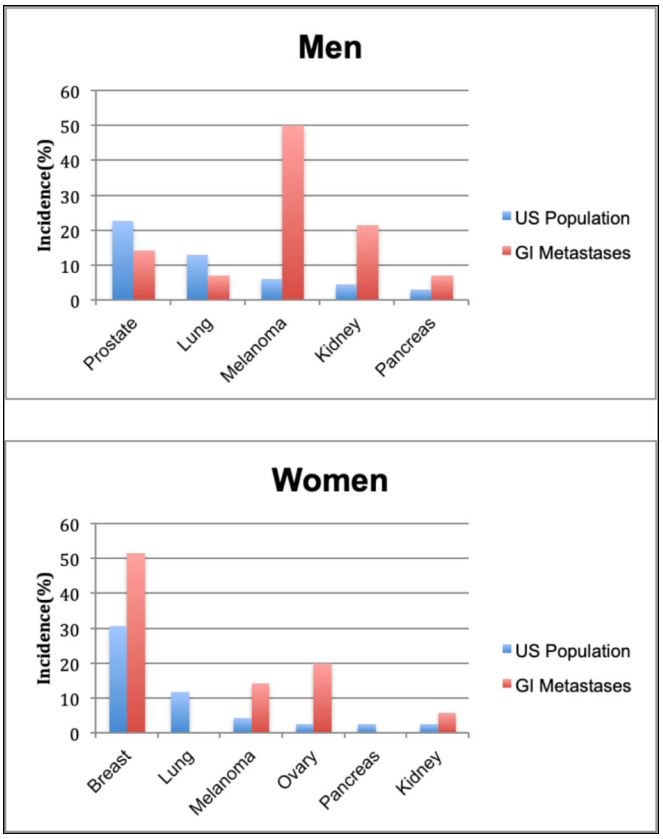

Figure 4. Incidence of gastrointestinal metastases compared to overall cancer incidence. **(a)** Relative incidence of various cancers in US men from 2012 to 2016 (blue bars) compared to relative incidence of gastrointestinal metastasis in our study from 2005 to 2018 (red bars). Melanoma and kidney cancer were overrepresented relative to their incidence, whereas prostate and lung cancer were underrepresented. **(b)** Data in US women. Breast, melanoma, ovarian, and kidney cancers were overrepresented, whereas lung and pancreatic cancers were underrepresented.

stomach cancers (15 cases), whereas we excluded primary stomach cancers in our study. Gilg et al's incidence of GI metastasis occurring via vascular spread (3.2 cases/year) is similar to the incidence in our study (3.5 cases/year). The retrospective design of our study was its primary weakness, because it limited the information that could be obtained due to differing levels of documentation across various patient charts. Furthermore, our study characterized the incidence of metastases to the GI tract presenting predominantly with GI symptoms in contrast to the incidence described in autopsy studies. Finally, our study evaluated the incidence of metastases to the GI tract detected via endoscopy, which mostly detects mucosal lesions. Therefore, serosal or mural metastases in the GI tract may be underrepresented in our study.

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In memoriam

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Dr. Daniel Polter, chief of gastroenterology at Baylor University Medical Center (BUMC) from 1971 to 2003, died on September 26, 2021. He was born in Chicago, Illinois, on December 17, 1933. When he was very young, he and his family moved to Norman, Oklahoma, and then to Dallas, Texas. He graduated from the University of Texas in Austin in 1955, majoring in chemistry, and from the University of Texas Southwestern Medical School in 1959. His internship, residency, and chief residency in internal medicine were at Parkland Memorial Hospital in Dallas. From 1963 to 1965, he was in the Medical Corps of the US Army, stationed in Orleans, France. Thereafter, he spent 1 year in fellowship in gastroenterology at the Wadsworth Veterans Administration Hospital in Los Angeles, returning to Dallas in 1966 as chief of gastroenterology at the VA Hospital. Four years later, he entered private practice and in 1971 became chief of gastroenterology at BUMC. During his years at BUMC, he spearheaded the inception of its liver transplant program and chaired the transplant selection committee from 1985 to 1992. He also served as president of BUMC Medical Staff (1990–1991) and chairman of the Medical Board (1991–1992). Dr. Polter was a founding member of Digestive Health Associates of Texas, one of the largest gastroenterology practices in the country. In 1996, he was awarded the Distinguished Clinician Award of the American Gastroenterological Association. From 1998 until 2000, he was president of the Texas Society for Gastroenterology and Endoscopy; that organization gave him the Robert Nelson–Marcel Patterson Award in 2003. Dr. Polter was an editorial board member of *BUMC Proceedings* for many years. A full interview with him is available in the journal at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1200651/.